IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jane Hirsh, Roman V. Rariy, and Michael Heffernan		
Serial No.:	10/690,872	Group Art Unit:	1618
Filed:	October 22, 2003	Examiner:	Leah H. Schlientz
For:	*PULSATILE RELEASE COMPOSITIONS OF MILNACIPRAN*		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

The undersigned, Dr. Martin Keller, does hereby declare and state that:

1. I am the Mary E. Zucker Professor and Chairman of the Department of Psychiatry and Human Behavior at Brown Medical School in Providence, RI, as well as Psychiatrist-in-Chief at Butler Hospital and Executive Psychiatrist-in-Chief at the six Brown Medical School affiliated hospitals. I have received more than 20 research grant awards from the NIH and numerous grants from research foundations and the pharmaceutical industry. I am the recipient of the 1998 National Alliance for Research on Schizophrenia and Depression (NARSAD) Lieber award for research on the causes, pathophysiology, treatment, and prevention of depression. I was awarded the 1999 Klerman Lifetime Research Award from the National Depression and Manic Depression Association. I was also the recipient of the 2001 American College of Psychiatrists Mood Disorders Lifetime Research Award for major research contributions to the

understanding and treatment of mood disorders and 2005 Voice of Mental Health Award from The Jed Foundation for contributions in the area of suicide prevention. My CV is attached as Appendix A.

2. This application is assigned to Collegium Pharmaceutical. I have not been paid to render this opinion nor am I an inventor or direct beneficiary of this application. However, I have a small financial interest in Collegium Pharmaceutical as an owner of less than 0.3% of the outstanding shares of the company.

3. Collegium has asked me to render an opinion on why the Pulsatile Release Milnacipran formulation defined by the claims in U.S.S.N. 10/690,872 filed October 22, 2003 is not obvious over the prior art cited by the Examiner. In order to render this opinion, I have reviewed the published patent application (Appendix B), the claims in the amendment and response filed June 1, 2007 (Appendix C), and the Office Action mailed August 3, 2007 and references cited therein (Appendix D).

4. Milnacipran is an antidepressant that has been used extensively in Europe and Japan and is currently being developed in the United States by Cypress Bioscience, Inc. for the treatment of fibromyalgia. Cypress has demonstrated that twice-a-day administration of immediate release formulation in a fibromyalgia trial resulted in pain relief statistically superior to that of placebo treatment (Cypress Bioscience Inc., Cypress Bioscience Inc. Announces Final Results of Milnacipran Phase II Clinical Trial in Fibromyalgia, Media Release, Mar. 21, 2003). Once-a-day administration, however, is highly desired due to patient compliance issues and is the standard of therapy in the depression and chronic pain markets. Milnacipran is not currently commercially available in a once-daily dosage form. Traditionally, when a once-a-day formulation of a

drug with a fairly short half-life (8 hours in case of milnacipran) is desired, developing an extended release formulation would normally be the choice of a person of ordinary skill in the art. An extended or sustained release formulation results in a long-lasting slow and relatively regular release of the active ingredient over time. This is not a pulsatile release formulation. A pulsatile release formulation is characterized by an immediate release of a first dose of drug upon ingestion followed by a period of no release, followed by release of a delayed release dose of the drug. Alternatively, both pulses can be delayed to release milnacipran at different times after ingestion of the dosage form.

Given the *demonstrated* effectiveness of milnacipran administered twice-a-day in two separated doses of the immediate release formulation, as shown in an earlier Phase II trial and in the recently completed Phase III clinical trial in fibromylagia (http://www.cypressbio.com/news/releases/20070522-1.pdf), a once-a-day formulation that mimics this pharmacokinetic pattern as closely as possible has the best chance of providing the same therapeutic effect as seen in the aforementioned clinical trials. Providing milnacipran in a once-a-day formulation that has two separate and distinct "pulses" or releases of drug offers to a patient compliance benefit at the same time providing a pharmacokinetic profile that closely mimics that of a twice-a-day immediate release formulation.

5. It was not obvious as of December 2002, that pulsatile release formulations of milnacipran could be developed that would produce an efficacious dose over approximately 24 hours. In the formulations developed by the inventors, the immediate release dosage unit comprises a first dose of an active agent that is released substantially immediately following oral administration of the dosage form to a patient. The delayed

release dosage unit comprises a second dose of the active agent and a means for delaying release of the second dose for approximately 3 hours to less than 14 hours following oral administration of the dosage form. These release times indicate that milnacipran will be released from the formulations in disparate gastrointestinal (GI) segments. Drug absorption is known to differ significantly in various GI segments. Physiological factors such as GI transit time, regional pH, surface area, enzymatic activity, manner of transport (i.e., passive vs. active) and microflora, all contribute to the variability in absorption (*see*, Rouge, et al., *Int. J. Pharma.*, 136:117-139 (1996), attached). In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine and colon. However, individual drugs can vary widely in their GI absorption spectra. Given the wide range of absorption spectra for drugs in different segments of the GI and the inability to predict these absorption spectra from preclinical models, it was not obvious that pulsed release formulations of milnacipran would be able to provide an efficacious dose over approximately 24 hours.

5. Only through a careful understanding of the relationship between the drug's chemical and physical properties and its absorption in the lower parts of the human gastrointestinal tract can a dosage form that releases drug in two separate pulses be designed. For many drugs, *including* milnacipran, their absorption in the lower intestine is not known and thus those of ordinary skill in the art would **not** have been motivated to design and manufacture a dosage form which relies on complete absorption of the second release (i.e., pulse or dose) of milnacipran several hours after ingestion. The pulsatile release formulations developed by Collegium and their pharmacokinetic profiles are generally demonstrated by reference to the data attached in Appendix E. This data

demonstrates the surprising finding that the second release ("pulse") of milnacipran is *fully absorbed* several hours after ingestion and establishes that the presently claimed once-a-day pulsatile release formulations are effective to deliver plasma levels of milnacipran considered to be in the effective range for the treatment of Fibromylagia.

6. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

12/14/07
Date

Martin Keller
Dr. Martin Keller

Appendix C: Amendment and response filed June 1, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jane Hirsh, Roman V. Rariy, and Michael Heffernan

Serial No.: 10/690,872 Art Unit: 1618

Filed: October 22, 2003 Examiner: Schlientz, Leah H.

For: *PULSATILE RELEASE FORMULATIONS OF MILNACIPRAN*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

Sir:

Responsive to the Office Action mailed on March 26, 2007, please amend the application as follows. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

Amendment

In the Claims

1. (previously presented) A milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects.

2. (original) The milnacipran formulation of Claim 1, wherein the side effect is nausea.

3. (original) The milnacipran formulation of Claim 1, wherein the side effects are selected from the group consisting of vomiting, headache, tremulousness, anxiety, panic attacks, palpitations, urinary retention, orthostatic hypotension, diaphoresis, chest pain, rash, weight gain, back pain, constipation, vertigo, increased sweating, agitation, hot flushes, tremors, fatigue, somnolence, dyspepsia, dysoria, nervousness, dry mouth, abdominal pain, irritability, and insomnia.

4. (original) The milnacipran formulation of Claim 1 comprising:

(a) an immediate release dosage unit comprising a first dose of the active agent that is released substantially immediately following oral administration of the dosage form to a patient resulting in the first plasma level peak at approximately 0.05 hours to less than 3 hours following oral administration;

(b) a delayed release dosage unit comprising a second dose of the active agent and a means for delaying release of the second dose resulting in the second plasma level peak at approximately 3 hours to less than 14 hours following oral administration of the dosage form; and optionally

(c) a second delayed release dosage unit comprising a third dose of the active agent and a means for delaying release of the third dose resulting in the third plasma level peak at approximately 5 hours to less than 18 hours following oral administration of the dosage form.

5. (original) The milnacipran formulation of claim 4, wherein an enteric coating is added to the formulation and the release profile is further characterized by a 0.05-4 hours lag time period during which less than approximately 10% of the first "pulse" milnacipran dose is released followed by a complete release of the first "pulse".

6. (original) The milnacipran formulation of Claim 1 providing milnacipran blood plasma levels that are characterized by Cmax below approximately 3000 ng/ml.

7. (original) The milnacipran formulation of Claim 6 providing milnacipran blood plasma levels that are characterized by Cmax below approximately 2000 ng/ml.

8. (original) The milnacipran formulation of Claim 6 providing milnacipran blood plasma levels that are characterized by C max below approximately 1000 ng/ml.

9. (original) The milnacipran formulation of Claim 1 further comprising at least one other active compound selected from the group consisting of analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, anxioltyics, sedatives, hypnotics, antipsychotics, bronchodilators, anti asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics, and anti-narcoleptics.

10. (original) The milnacipran formulation according to claim 9, comprising one or more compounds selected from the group consisting of aceclofenac, acetaminophen,

adomexetine, almotriptan, alprazolam, amantadine, amcinonide, aminocyclopropane, amitriptyline, amolodipine, amoxapine, amphetamine, aripiprazole, aspirin, atomoxetine, azasetron, azatadine, beclomethasone, benactyzine, benoxaprofen, bermoprofen, betamethasone, bicifadine, bromocriptine, budesonide, buprenorphine, bupropion, buspirone, butorphanol, butriptyline, caffeine, carbamazepine, carbidopa, carisoprodol, celecoxib, chlordiazepoxide, chlorpromazine, choline salicylate, citalopram, clomipramine, clonazepam, clonidine, clonitazene, clorazepate, clotiazepam, cloxazolam, clozapine, codeine, corticosterone, cortisone, cyclobenzaprine, cyproheptadine, demexiptiline, desipramine, desomorphine, dexamethasone, dexanabinol, dextroamphetamine sulfate, dextromoramide, dextropropoxyphene, dezocine, diazepam, dibenzepin, diclofenac sodium, diflunisal, dihydrocodeine, dihydroergotamine, dihydromorphine, dimetacrine, divalproxex, dizatriptan, dolasetron, donepezil, dothiepin, doxepin, duloxetine, ergotamine, escitalopram, estazolam, ethosuximide, etodolac, femoxetine, fenamates, fenoprofen, fentanyl, fludiazepam, fluoxetine, fluphenazine, flurazepam, flurbiprofen, flutazolam, fluvoxamine, frovatriptan, gabapentin, galantamine, gepirone, ginko bilboa, granisetron, haloperidol, huperzine A, hydrocodone, hydrocortisone, hydromorphone, hydroxyzine, ibuprofen, imipramine, indiplon, indomethacin, indoprofen, iprindole, ipsapirone, ketaserin, ketoprofen, ketorolac, lesopitron, levodopa, lipase, lofepramine, lorazepam, loxapine, maprotiline, mazindol, mefenamic acid, melatonin, melitracen, memantine, meperidine, meprobamate, mesalamine, metapramine, metaxalone, methadone, methadone, methamphetamine, methocarbamol, methyldopa, methylphenidate, methylsalicylate, methysergid(e), metoclopramide, mianserin, mifepristone, milnacipran, minaprine, mirtazapine,

moclobemide, modafinil, molindone, morphine, morphine hydrochloride, nabumetone, nadolol, naproxen, naratriptan, nefazodone, neurontin, nomifensine, nortriptyline, olanzapine, olsalazine, ondansetron, opipramol, orphenadrine, oxaflozane, oxaprazin, oxazepam, oxitriptan, oxycodone, oxymorphone, pancrelipase, parecoxib, paroxetine, pemoline, pentazocine, pepsin, perphenazine, phenacetin, phendimetrazine, phenmetrazine, phenylbutazone, phenytoin, phosphatidylserine, pimozide, pirlindole, piroxicam, pizotifen, pizotyline, pramipexole, prednisolone, prednisone, pregabalin, propanolol, propizepine, propoxyphene, protriptyline, quazepam, quinupramine, reboxitine, reserpine, risperidone, ritanserin, rivastigmine, rizatriptan, rofecoxib, ropinirole, rotigotine, salsalate, sertraline, sibutramine, sildenafil, sulfasalazine, sulindac, sumatriptan, tacrine, temazepam, tetrabenozine, thiazides, thioridazine, thiothixene, tiapride, tiasipirone, tizanidine, tofenacin, tolmetin, toloxatone, topiramate, tramadol, trazodone, triazolam, trifluoperazine, trimethobenzamide, trimipramine, tropisetron, valdecoxib, valproic acid, venlafaxine, viloxazine, vitamin E, zimeldine, ziprasidone, zolmitriptan, zolpidem, zopiclone and isomers, salts, and combinations thereof.

11. (original) The milnacipran formulation of Claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of dextrogyral or levrogyral enantiomers of the milnacipran or pharmaceutically acceptable salts thereof.

12. (original) The milnacipran formulation of Claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of a mixture of milnacipran enantiomers or pharmaceutically acceptable salts thereof.

13. (previously presented) The milnacipran formulation of Claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of an active metabolite of milnacipran or pharmaceutically acceptable salts thereof.

14. (original) The milnacipran formulation of Claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (F2782) or pharmaceutically acceptable salts thereof.

15. (original) The milnacipran formulation of Claim 1 further comprising an enteric coating.

16. (original) The milnacipran formulation of Claim 1, wherein the administrable milnacipran unit dose is from 25 to 500 mg.

17. (original) The milnacipran formulation of Claim 1, wherein the administrable milnacipran unit dose is from 200 to 500 mg.

18. (original) The milnacipran formulation of Claim 14 comprising 25 to 500 mg milnacipran and 100 to 600 mg modafinil.

19. (original) The milnacipran formulation of claim 1 comprising a mixture of beads or particles releasing drug at different times.

20. (original) A kit comprising the milnacipran formulation of Claim 1.

21. (original) The kit of Claim 20 comprising different dosage units of milnacipran to allow for dosage escalation.

22. (original) The kit of Claim 20 comprising instruction on taking the formulation once daily before bedtime.

23. (canceled)

24. (canceled)

Remarks

Claims 23 and 24 have been canceled.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 13 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

The Legal Standard

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). See also *In re Larsen*, No. 01-1092 (Fed. Cir. May 9, 2001) (unpublished). See also *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, 71 USPQ2d 1081, 1089 (Fed. Cir. 2004) ("The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles....Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite.").

Analysis

Claim 13 is directed to the milnacipran formulation of Claim 1, wherein the milnacipran is in the form of a therapeutically equivalent dose of an active metabolite of milnacipran or pharmaceutically acceptable salts thereof.

The Examiner alleges that claim 13 is indefinite because there is no guidance provided to demonstrate the chemical identity or physical characteristics of any compound which may be a milnacipran metabolite, nor is any guidance provided to describe what amount of the metabolite is to be included in the formulation. The Examiner is applying the incorrect legal standard for definiteness.

Exxon Research and Engineering Company v. United States, 265 F.3d 1371 (Fed. Cir. 2001), stated the standard to be as follows: "If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2." *Id.* citing *Miles Labs, Inc., v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1994).

The court further stated that claims do not have to be plain on their face to be definite. Rather, "the claims need be amenable to construction, however difficult that task may be. If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.*

Claim 13 specifies that the milnacipran is in the form of a therapeutically equivalent dose of an active metabolite of milnacipran or pharmaceutically acceptable salts thereof. The specification discloses that metabolism of milnacipran in the liver leads to the formation of ten chemically identified metabolites (page 34, lines 9-10). Puozzo *et al.*, *Eur. J. Drug. Metab. Pharmacikinet.*, Apr-Jun, 23(2), 273-279 (1998), a copy of which is enclosed, describes some of these 10 metabolites including glucuroconjugated phase I metabolites, N-mono-dealkylated metabolites, N-di-dealkylated metabolites, and hydroxylated metabolites (page 273). The specification also

discloses that the dosages of enantiomers, derivatives, and metabolites of milnacipran may need to be adjusted based on the relative activity of the racemic mixture of milnacipran (page 16, lines 29-31). One skilled in the art would understand the bounds of the term "metabolite" when read in light of the specification. Accordingly, claim 13 is definite.

Rejection Under 35 U.S.C. § 103

Claims 1-10, 15-17, and 19-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,340,476 to Midha *et al.* ("Midha"), in view of Ansseau *et al.*, *Psychopharmacology*, 114, 131-137, (1994) ("Ansseau"). Claims 1-10 and 15-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Midha in view of Ansseau and Menza *et al.*, *J. Clin. Psychiatry*, 61(5), 378-381 (2000) ("Menza"). Claims 1-13, 15-17, and 19-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Midha in view of Ansseau, further in view of WO 98/08495 to Paillard *et al.* ("Paillard"). Claims 1-3, 6-17, 20, and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0203055 to Rao *et al.* ("Rao"). Applicants respectfully traverse this rejection.

Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the

claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker* , 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The standard for obviousness under 35 U.S.C. 103 was recently reaffirmed by the U.S. Supreme Court in KSR Int'l. Co. v. Teleflex, Inc, 2007 U.S. LEXIS 4745; 75 U.S.L.W. 4289. According to the Supreme Court,

"often it will be necessary ... to look to interrelated teachings of multiple patents; the effects of demands known to design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

In response to this decision, on May 3, 2007, the Assistant Commissioner of the U.S. Patent Office Margaret Facarino sent to the Technology Center Directors a memo, stating in relevant part:

(1). The court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C §103(a). The four factual inquiries under *Graham* are:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of one of ordinary skill in the art; and

(d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966)

(2) The court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. §103(a).

(3) The court rejected the rigid application of the "teaching, suggestion or motivation" (TSM) test, which required a showing of some teaching, suggestion or motivation in the prior art that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter obvious.

(4) The court noted that the analysis supporting a rejection under 35 U.S.C §103(a) should be made explicit, and it was "important to identify a reason that would

have prompted a person of ordinary skill in the relevant art to combine the [prior art] elements" in the manner claimed.

"Therefore, in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed."

Analysis

Claim 1, and the claims dependent thereon, are directed to a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects.

Claim 20, and the claims dependent thereon, are directed to a kit containing the formulation of claim 1.

Claims 23 and 24 have been canceled.

Claims 1-10, 15-17, and 19-23 are not obvious over Midha in view of Ansseau

Claims 1-3, 9, 10, 15-17, and 19-23 are not obvious over Midha in view of Ansseau since the references, alone or in combination, do not disclose or suggest a pulsatile release milnacipran formulation which provides a therapeutic effect over 24 hours with reduced incidence or intensity of side effects

a. Midha

Midha describes pharmaceutical dosage forms for pulsatile release delivery of methylphenidate (available commercially as Ritalin®) ("abstract"). Ritalin® is a central

nervous system stimulant that is used for the treatment of Attention Deficit Disorder ("ADD") and Attention Deficit-Hyperactivity Disorder ("ADHD") (col. 2, lines 5-13). Midha is concerned with the pulsatile delivery of methylphenidate due to its potential for tolerance (i.e., loss of clinical efficacy when constant blood levels are maintained) short half-life, and potential for abuse. Milnacipran does not exhibit potential for tolerance or potential for abuse. Midha does not disclose or suggest a milnacipran formulation that provides pulsatile release of milnacipran which exhibits diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. In fact, Midha does not recognize that pulsatile release formulations can be used to minimize side effects.

Further, Midha teaches away from formulations that provide a therapeutic effect over 24 hours. Midha discloses that for pulsatile release formulations containing three doses of methylphenidate, the third dose should be lower than the first two due to the fact that methylphenidate can disrupt sleep (col. 8, lines 33-35) and thus the compositions described in Midha are not designed nor intended to provide a therapeutic effect over 24 hours.

b. Ansseau

Ansseau describes the efficacy and tolerance of fluoxetine versus milnacipran (abstract). Ansseau discloses that fluoxetine showed superior results versus milnacipran (page 135, first paragraph). Ansseau does not disclose or suggest a pulsatile release formulation of milnacipran that exhibits a therapeutic effect over 24 hours. In fact, Ansseau teaches away from the claimed composition since Ansseau discloses administering milnacipran in a single immediate release dose, which is unlikely to

provide a therapeutic effect over 24 hours. Ansseau discloses that the decreased efficacy of milnacipran was likely due to inadequate plasma levels.

Further, Ansseau does not disclose or suggest a pulsatile release milnacipran formulation which exhibits diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. Although Ansseau does mention side effects associated with milnacipran and fluoxetine, Ansseau discloses that more patients dropped out of the fluoxetine study due to adverse effects than dropped out of the milnacipran study (page 133, first column, last paragraph).

c. Midha in view of Ansseau

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

The Examiner alleges that it would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile release dosage form because Midha teaches that pulsatile release formulations are useful for drugs which have a short half-life and must otherwise be administered two or three times daily and Ansseau discloses that milnacipran has a relatively short half-life. The Examiner has not considered the entire disclosure of Midha. Midha discloses pulsatile release formulations of drugs that exhibit

the potential for tolerance and abuse, namely methylphenidate. Milnacipran does not possess either of these properties. Midha does not disclose or suggest a pulsatile release milnacipran formulation that exhibits a therapeutic effect over 24 hours. In fact, Midha teaches away from a formulation which provides a therapeutic effect over 24 hours since Midha discloses releasing a lower dose from the formulation due to methylphenidate's potential for disrupting sleep.

Ansseau describes comparative studies of *immediate release* milnacipran and fluoxetine formulations. Ansseau does not disclose or suggest a formulation providing a therapeutic effect over 24 hours. Ansseau discloses that milnacipran was less effective than fluoxetine and that this was likely due to the fact that only a single dose was administered, which led to inadequate plasma levels. Further, while Ansseau does briefly discuss the side-effects associated with milnacipran and fluoxetine, Ansseau does not disclose or suggest formulations which exhibit reduced incidence or intensity of side effects. Ansseau does not provide the elements missing from Midha.

Moreover, the Examiner has failed to show that one of ordinary skill in the art would not be motivated to combine the pulsatile release methylphenidate formulations of Midha with the immediate release milnacipran formulations of Ansseau to arrive at the claimed compositions since neither reference discloses or suggests pulsatile release formulations that provide a therapeutic effect over 24 hours with reduced the frequency or severity of side effects. Even if one were motivated to combine the references, one of ordinary skill in the art would be motivated to prepare pulsatile release formulations containing fluoxetine, which showed superior results according to Ansseau. Finally, the Examiner has failed to show that one of ordinary skill in the art would have a reasonable

expectation of success. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness. Claims 1-3, 8, 9, 15-17, and 19-22 are not obvious over Midha and Ansseau.

Claims 4-8 are not obvious over Midha in view of Ansseau since the references alone or in combination do not disclose or suggest the release profile and C_{max} value recited in the claims

The references, alone or in combination, do not disclose or suggest the pulsatile release formulation of claim 1 having the release profile specified in claim 4 and 5. Midha discloses the release profile for methyl phenidate, not milnacipran (col 5, lines 9-16). Midha does not disclose the C_{max} values recited in claims 6-8. Ansseau does not disclose the elements missing from Midha. The references, alone or in combination, do not recite all the elements of the claims. The Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, claims 4-8 are not obvious over Midha in view of Ansseau.

Claims 1-10 and 15-23 are not obvious over Midha in view of Ansseau further in view of Menza *et al., J. Clin. Psychiatry*, 61(5), 378-81 (2000) ("Menza")

Claims 1-3, 9, 10, and 15-23 are not obvious over Midha in view of Ansseau and Menza since the references alone or in combination do not disclose or suggest a pulsatile release milnacipran formulation which provides a therapeutic effect over 24 hours with reduced incidence or intensity of side effects

a. Midha and Ansseau

Midha and Ansseau are discussed above. Midha and Ansseau, alone or in combination, do not disclose or suggest a pulsatile release milnacipran formulation

providing a therapeutic effect over 24 hours with reduced incidence or intensity of side effects.

b. Menza

Menza describes administering modafinil to augment a partial or nonresponse to an antidepressant (abstract). Menza does not disclose or suggest administering modafinil in combination with a pulsatile release milnacipran formulation as required by claim 1 and the claims dependent thereon. Menza does not provide the elements missing from Midha and Ansseau. One of ordinary skill in the art would not be motivated to combine Midha, Ansseau, and Menza to arrive at the claimed compositions. The Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, claims 1-3, 9, 10, and 15-22 are not obvious over Midha in view of Ansseau and Menza.

Claims 4-8 are not obvious over Midha in view of Ansseau and Menza since the references alone or in combination do not disclose or suggest the release profile and C_{max} value recited in the claims

a. Midha in view of Ansseau further in view of Menza

As discussed above, Midha and Ansseau, alone or in combination, do not disclose or suggest the pulsatile release formulation of claim 1 having the release profile specified in claim 4 and 5 nor the C_{max} values recited in claims 6-8. Menza does not provide the elements missing from Midha and Ansseau. In fact, Menza is silent regarding release profiles since the formulation described in Menza is an immediate release formulation, not a pulsatile release formulation. One of ordinary skill in the art would be motivated to combine the pulsatile release methylphenidate formulation of Midha with the immediate release formulations of Ansseau and Menza to arrive at the claimed compositions. The

Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, claims 4-8 are not obvious over Midha in view Ansseau further in view of Menza.

Claims 1-13, 15-17, and 19-24 are not obvious over Midha in view of Ansseau and WO 98/08495 by Paillard *et al.* ("Paillard")

Claims 1-3, 9, 10-12, 15-17, and 19-24 are not obvious over Midha in view of Ansseau and Paillard since the references, alone or in combination, do not disclose or suggest a pulsatile release milnacipran formulation which provides a therapeutic effect over 24 hours with reduced incidence or intensity of side effects

a. Midha and Ansseau

Midha and Ansseau are discussed above. Midha and Ansseau, alone or in combination, do not disclose or suggest a pulsatile release milnacipran formulation providing a therapeutic effect over 24 hours with reduced incidence or intensity of side effects.

b. Paillard

Paillard describes a prolonged release pharmaceutical composition, for oral administration, containing a single daily dose of 60 to 140 mg of milnacipran (abstract). Paillard does not disclose a pulsatile release formulation as required by the claims.

c. Midha in view of Ansseau and Paillard

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. Midha in view of Ansseau and does not disclose or suggest a pulsatile release milnacipran formulation which provides a therapeutic effect over 24 hours with reduced incidence or intensity of side effects. Paillard does not disclose the elements missing from Midha and Ansseau.

Further, one of ordinary skill in the art would not be motivated to combine the pulsatile release methylphenidate compositions of Midha with the immediate release milnacipran formulation of Ansseau and the extended release formulation of Paillard to arrive at the claimed compositions. The Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, claims 1-3, 9, 10-12, 15-17, and 19-22 are not obvious over Midha in view of Ansseau and Paillard.

Claims 4-8 are not obvious over Midha in view of Ansseau and Paillard since the references alone or in combination do not disclose or suggest the release profile and C_{max} value recited in the claims

As discussed above, Midha and Ansseau, alone or in combination, do not disclose or suggest the pulsatile release formulation of claim 1 having the release profile specified in claim 4 and 5 nor the C_{max} values recited in claims 6-8. Paillard does not provide the elements missing from Midha and Ansseau. One of ordinary skill in the art would be motivated to combine the pulsatile release methylphenidate formulation of Midha with the immediate release formulation of Ansseau and the extended release formulation of Paillard to arrive at the claimed compositions. The Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, claims 4-8 are not obvious over Midha in view Ansseau and Paillard.

Claims 1-3, 6-17, 20, and 23 are not obvious over U.S. Patent Application Publication No. 2003/0203055 to Rao *et al.* ("Rao")

Rao describes methods of treating visceral pain syndromes in a mammal (abstract). The method includes administering to the mammal an effective amount of a selective norepinephrine (NE)-serotonin (5-HT) reuptake inhibitor (NSRI), such as

milnacipran (abstract). Rao does not disclose or suggest a pulsatile release milnacipran formulation.

A pulsatile release dosage form is one that mimics a multiple dosing profile without repeated dosing and allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form) (page 9, lines 5-11). A pulsatile release profile is characterized by a first dose of drug that is released substantially immediately following administration, followed by a period of no release followed by release of a first, and optionally a second, delayed release dose (page 9, lines 13-16). Pulsatile release is not the same thing as prolonged release.

The Examiner alleges that the formulation described in Example 41 is a pulsatile release formulation. The Examiner is incorrect. Example 41 in Rao describes a formulation containing immediate release and sustained release (i.e., extended release) doses. The formulation "results in a long-lasting slow and relatively regular release of the active ingredient" (page 25, paragraph 0361). This is not a pulsatile release formulation. As discussed above, a pulsatile release formulation is characterized by a first dose of drug followed by a period of no release, followed by release of a delayed release dose, etc. Rao does not disclose each and every element of the claims. Accordingly, claims 1-3, 6-17, and 20 are not obvious over Rao.

Double Patenting Rejection

Claims 1-9 and 11-24 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 10-28 of copending Application Serial No. 11/192,697. Applicants respectfully traverse

this rejection to the extent it is applied to the claims as amended. Claims 1-3, 6-18, and 20-24 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-18, and 20-24 of copending Application Serial No. 10/691,936 in view of Midha further in view of Ansseau. Applicants respectfully traverse this rejection. Claim 14 was rejected on the grounds of nonstatutory obviousness type double patenting over claims 1-3 and 9 of U.S. Patent No. 7,038,085 in view of Midha and Ansseau. Applicants respectfully traverse this rejection.

Legal Standard

Before consideration can be given to the issue of double patenting, two or more patents or applications must have at least one common inventor and/or be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3) pursuant to the CREATE Act (Pub. L. 108-453, 118 Stat. 3596 (2004)). Congress recognized that the amendment to 35 U.S.C. 103(c) would result in situations in which there would be double patenting rejections between applications not owned by the same party (see H.R. Rep. No. 108-425, at 5-6 (2003)). For purposes of a double patenting analysis, the application or patent and the subject matter disqualified under 35 U.S.C. 103(c) as amended by the CREATE Act will be treated as if commonly owned. See also MPEP § 804.03. Since the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis.

Analysis

Claims 23 and 24 have been canceled. These claims will be pursued in copending Application No. 11/192,697. Claims 1-22 in U.S.S.N. 10/690,872 will be canceled. Accordingly, the Examiner's rejection under 35 U.S.C. § 101 is no longer applicable.

The double patenting rejection of claims 1-3, 6-19, and 20-24 as being patentable over claims 1-3, 6-18, and 20-24 of copending U.S.S.N. 10/691,936 in view of Midha and Ansseau is legally improper

The claims of the present application are directed to a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. In contrast, the claims of the '936 application are directed to a delayed release or extended release formulation of milnacipran.

The Examiner admits that the claims of the '936 application are not directed to pulsatile release milnacipran formulations (*see* page 15, second paragraph of the office action). However, the Examiner then goes on to cite the disclosures of Midha and Ansseau in an attempt to provide the elements missing from the claims. This is an obviousness analysis, not a double patenting analysis and is legally improper.

As discussed above, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis. As the Examiner admitted, the present claims are directed to pulsatile release formulations and the claims of the '936 application are directed to extended release formulations. Pulsatile release does not encompass extended release.

A "pulsatile release dosage form", as defined on page 16 of the specification, refers to a form that (1) mimics a multiple dosing profile without repeated dosing and (2) allows at least a two-fold reduction in dosing frequency as compared to that drug presented as a conventional dosage form. The passage on page 16 goes onto state that a pulsatile release profile is characterized by a time period of no release (lag time) followed by rapid drug release. On page 8, lines 24-25, the specification discloses that the compositions are characterized by an initial rapid release of a therapeutically effective dose of milnacipran followed by so-called "delayed release" pulses such that a second and optional third delayed dose of the active agent are released from the dosage form. If a third dose is incorporated into the form, it is released after a period of no release (lag time) following release of the second dose. These delayed release pulses can be released immediately or can be released over an extended period of time. This definition does not encompass delayed release or extended release formulations, neither of which have an initial rapid release of a therapeutically effective dose of milnacipran, followed by a period of no release (lag time), followed by "delayed release" pulses such that a second and optional third delayed dose of the active agent is released from the dosage form.

Accordingly, claims 1-3, 6-19, and 20-24 are patentable over claims 1-3, 6-18, and 20-24 of copending U.S.S.N. 10/691,936.

The double patenting rejection of claim 14 over claims 1-3 and 9 of U.S. Patent No. 7,038,085 in view of Midha further in view of Ansseau is legally improper

The claims of the present application are directed to a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished

incidence or reduced intensity relative to one or more immediate release milnacipran side effects. In contrast, the claims of the '085 patent are directed to an isolated compound of formula A and B, respectively. The claims of the '085 patent do not define a pulsatile release formulation.

The Examiner admits that the claims of the '085 patent are not directed to pulsatile release milnacipran formulations (*see* page 17, second paragraph of the office action). However, the Examiner then goes on to cite the disclosures of Midha and Ansseau in an attempt to provide the elements missing from the claims. This is an obviousness analysis, not a double patenting analysis, and is legally improper. In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is — does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? None of the claims in the '085 patent cited by the Examiner are directed to a pulsatile release formulation. Accordingly, claim 14 is patentable over claims 1-3 and 9 the '085 patent in view of Midha and Ansseau.

Allowance of claims 1-22, as amended, is respectfully solicited.

Respectfully submitted,

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Date: June 1, 2007

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Appendix E: Additional data provided by Collegium with respect to a pulsatile milnacipran formulation

Example 1: Preparation of an Alternative Immediate Release Milnacipran Tablet

The ingredients, manufacturing process, and tablet parameters for the immediate release portion of an alternative pulsatile release milnacipran formulation, referred to as Lot #5, are described below.

Ingredient	**Quantity per tablet, mg**	**Quantity per 7,000 tablets, g**
Milnacipran HCl	50.00	350
Microcrystalline Cellulose (Avicel® PH 102)	10.00	70
Pre-gelatinized Starch (Starch® 1500)	10.00	70
Purified Water	QS	
Magnesium Stearate	0.7	4.9

The following manufacturing procedure was used for the preparation of a Pilot Scale batch of Immediate Release Milnacipran tablets (Lot# 5):

Step 1: Sifting

Milnacipran hydrochloride, Avicel® PH102, and Starch® 1500 were sifted through a #40 mesh screen.

Step 2: Dry mixing

The sifted material from Step 1 was loaded into a V-cone blender and mixed for 10 minutes without an intensifier bar.

Step 3: Granulation

The dry mix from step 2 was granulated with purified water in a planetary mixer and the resulting wet mass was passed through a #12 mesh screen.

Step 4: Drying

The wet mass from step 3 was dried in a tray oven at 50°C until the moisture content was below 1%.

Step 5: Milling

The dried granules from step 4 were passed through #30 mesh screen.

Step 6: Lubrication

Magnesium stearate was sifted through a #40 mesh screen and added to the granules obtained in Step 5. The mixture was mixed in a V-Cone blender for 5 minutes without an intensifier bar.

Step 7: Compression

The blend from step 6 was compressed into tablets with average tablet weight of 70.7 mg using a 4.76 mm round standard concave punch at a hardness of 6-8 kP.

Tablet parameter	**Lot# 5**
Weight (mg)	70 - 72
Thickness (mm)	4.13 - 4.18
Friability (%)	0.113
Disintegration time in water	5 minutes 5 seconds

Example 2: Pilot scale preparation of a Delayed Release Portion of Pulsatile Release Milnacipran Formulation

Lot# 5 immediate release tablets were used for preparation of a delayed release dosage form. The manufacturing procedure consisted of spraying an isopropyl alcohol based coating suspension onto the immediate release tablets fluidized in the fluid bed processor. Tablets were collected with the following coat weight gain: 10% (Lot# 6), 15% (Lot# 7), and 20% (Lot# 8). After the coating process was completed, the tablets were incubated ("cured") at 40°C for 2 hours in the oven drier. The ingredients and preparation procedure of isopropyl alcohol-based coating suspension are given below.

Ingredients of isopropyl alcohol based coating suspension (Eudragit® L 100/S 100 blended in a ratio of 1 to 3 (w/w) L 100 to S 100).

Ingredient	**Quantity per batch, g**
Eudragit L 100	15
Eudragit S 100	45
Isopropyl alcohol	854
Purified water	50
Triethyl citrate	6
Talc	30

Suspension preparation procedure :

Eudragit® L 100 and Eudragit® S 100 were weighed and added to Isopropyl alcohol with stirring. Purified water was added to the solution. The solution was stirred until it became clear and triethyl citrate was added to the solution. The solution was stirred for 30 minutes at room temperature. Talc was added to the solution to form a suspension and the suspension was stirred for 5 minutes. The suspension was continually stirred during the coating process.

The following coating parameters were used:

Coating equipment	Fluid bed processor
Blower speed	2100 rpm
Spray rate	3 g / min
Inlet temp.	38°C
Tablet bed temp	36°C
Exhaust temp.	33°C
Spray	Continuous spray
Pressure	2 kg / cm^2

Tablets with 10% coat weight gain (Lot# 6) had the following parameters: 75 – 80 mg weight, 4.73 – 4.76 mm diameter, 4.18 – 4.31 mm thickness, and 7-9 kP hardness.

In vitro drug release studies were conducted using a USP dissolution apparatus II (paddles) at 50 rpm. Experiments were conducted in dissolution media at a temperature of 37.0±0.5°C, first for 2 hours in 0.1 N hydrochloric acid, followed by 5 hours in pH 6.8 phosphate buffer, and then 4 hours in pH 7.0 phosphate buffer. Samples were periodically withdrawn and analyzed for milnacipran content using HPLC. The dissolution results for Lots# 6, 7, and 8 are shown in Figure 1.

Example 3: Pharmacokinetic Parameters of Delayed Released Milnacipran tablet (Lot# 6) in Healthy Human Volunteers

The milnacipran delayed release tablet (10% coating weight gain, Lot# 6) described in Example 2 was tested in a single dose one way 6-patient pilot bioavailability study under fasting conditions.

The average milnacipran plasma concentration for five subjects as a function of time after tablet administration is shown in Figure 2. Average pharmacokinetic parameters were obtained by determining the pharmacokinetic parameters for each individual study subject and subsequently averaging the values obtained. The calculated pharmacokinetic parameters were as follows: T_{max} is 7±2 hours, C_{max} is 100±20 ng/ml, AUC (0-24) is 1043±218 ng hr/ml, and AUC (0-inf) is 1303±304 ng hr/ml (Note that the

data for five subjects were used to calculate the values above. The data for the 6th subject were not taken into account due to unexplainably low observed milnacipran plasma levels).

An IR milnacipran formulation was previously tested under fed conditions and it was found that the administration of 50 mg Milnacipran HCl capsule BID resulted in an AUC (0-24) equal to 2592 ng hr/ml, and an AUC (0-inf) equal to 2743 ng hr/ml. Although no direct comparison can be made with the data obtained in the current study due to different study conditions (fasting vs. fed), the AUC for 50 mg DR tablet given QD is essentially one half of that for 50 mg IR BID. This fact indicates that essentially all milnacipran released from DR tablet was absorbed in the GI tract despite the fact that drug release was delayed for several hours.

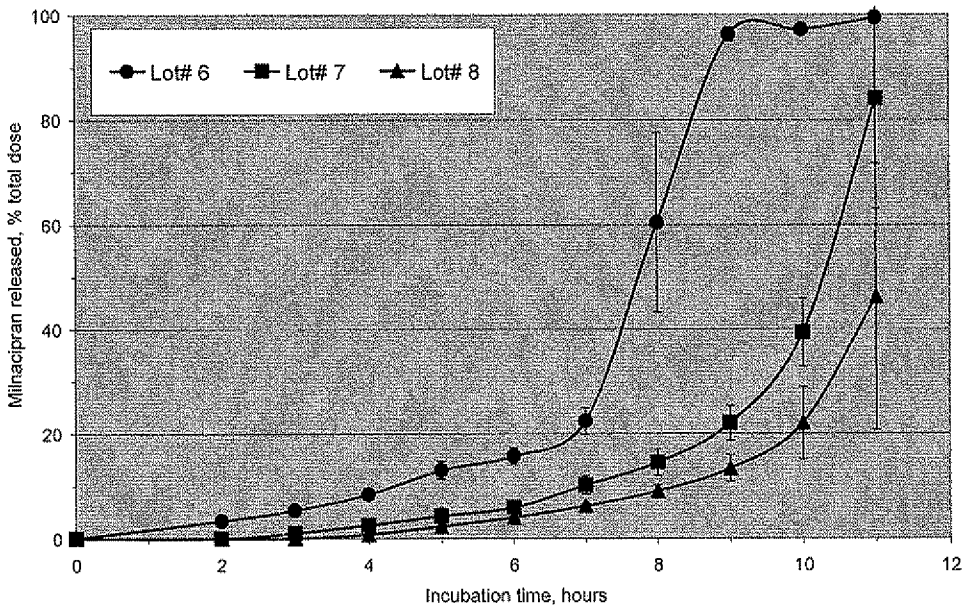

Figure 1. *In vitro* dissolution results for 50 mg milnacipran HCl delayed release tablet.

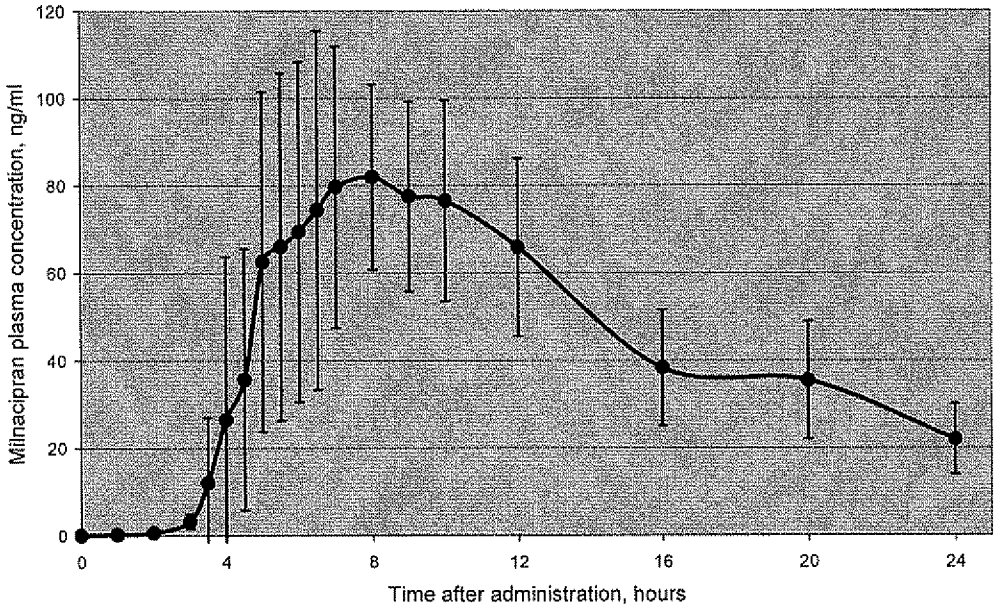

Figure 2. Pharmacokinetics of Delayed Released Milnacipran tablet in Healthy Human Volunteers.